FILE 'REGISTRY' ENTERED AT 13:08:58 ON 06 SEP 2002

L1 STRUCTURE UPLOADED

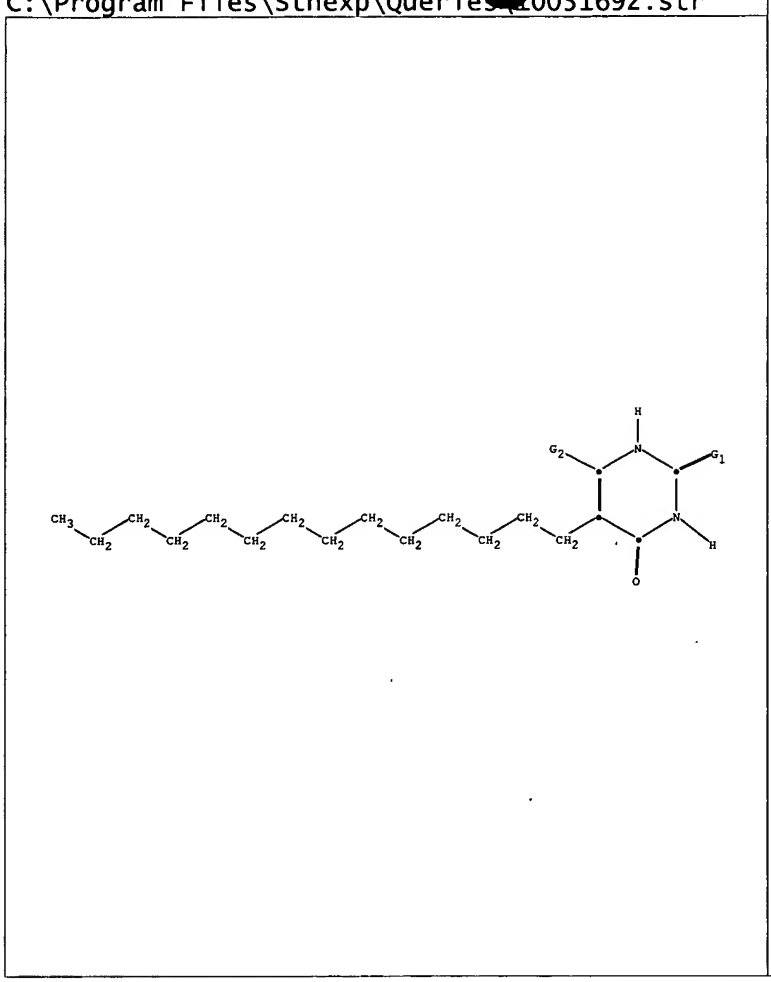
L2 1 S L1 SSS SAM

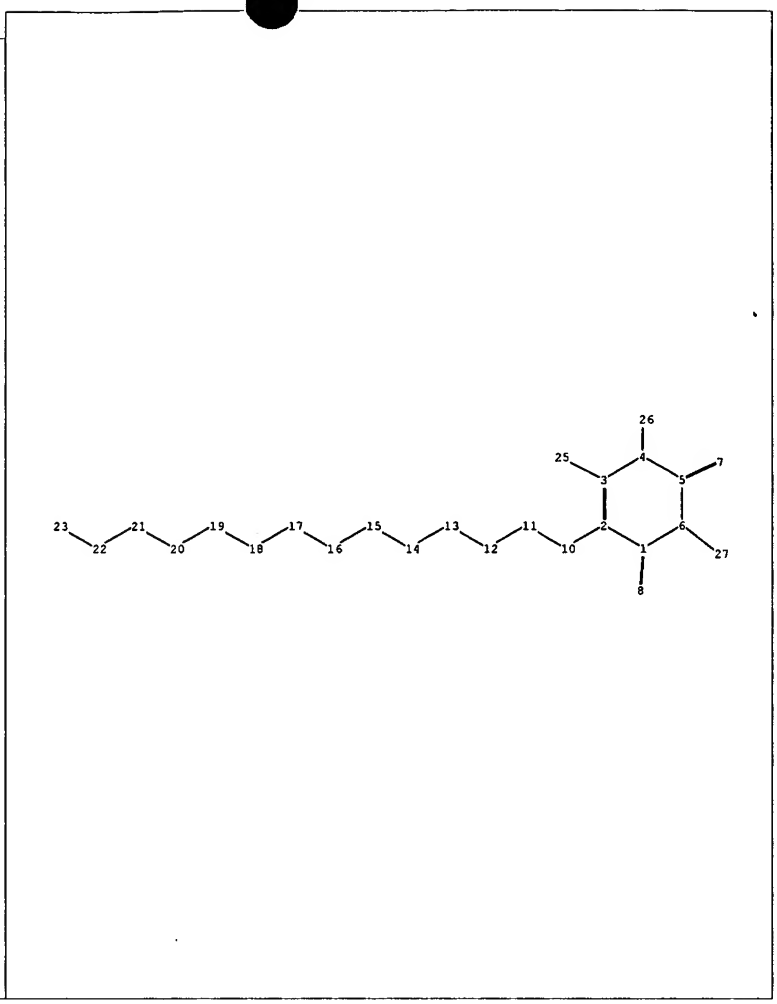
L3 6 S L1 SSS FULL

FILE 'CAPLUS' ENTERED AT 13:11:34 ON 06 SEP 2002

L4 2 S L3

C:\Program Files\Stnexp\Queries\10031692.str





chain nodes :
7 8 10 11 12 13 14 15 16 17 18 19 20 21 22 23 25 26 27
ring nodes :
1 2 3 4 5 6
chain bonds :
1-8 2-10 3-25 4-26 5-7 6-27 10-11 11-12 12-13 13-14 14-15 15-16 16-17 17-18
18-19 19-20 20-21 21-22 22-23
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6
exact/norm bonds :
1-2 1-6 1-8 2-3 3-4 3-25 4-5 5-6 5-7
exact bonds :
2-10 4-26 6-27 10-11 11-12 12-13 13-14 14-15 15-16 16-17 17-18 18-19 19-20
20-21 21-22 22-23

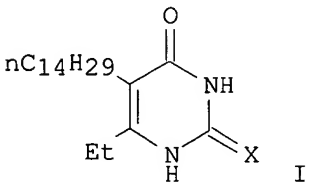
G1:O,S

G2:Et,n-Pr,i-Bu

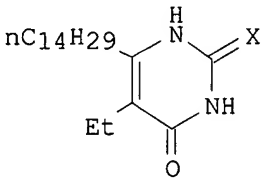
Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:CLASS 10:CLASS 11:CLASS
12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:CLASS 19:CLASS 20:CLASS
21:CLASS 22:CLASS 23:CLASS 25:CLASS 26:CLASS 27:CLASS

=> d l4 1-2 ibib abs

L4 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:719208 CAPLUS
DOCUMENT NUMBER: 136:53590
TITLE: Design, Synthesis, and Characterization of the Antitumor Activity of Novel Ceramide Analogues
AUTHOR(S): Macchia, Marco; Barontini, Silvia; Bertini, Simone; Di Bussolo, Valeria; Fogli, Stefano; Giovannetti, Elisa; Grossi, Enzo; Minutolo, Filippo; Danesi, Romano
CORPORATE SOURCE: Department of Pharmaceutical Sciences, University of Pisa, Pisa, 56126, Italy
SOURCE: Journal of Medicinal Chemistry (2001), 44(23), 3994-4000
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I



III

AB A deficiency in apoptosis is one of the key events in the proliferation and resistance of malignant cells to antitumor agents; for these reasons, the search for apoptosis-inducing drugs represents a valuable approach for the development of novel anticancer therapies. In this study we report the first example of conformationally restrained analogs of ceramide, where the polar portion of the mol. has been replaced by a thiouracil {[I; X = S (II)], [III; X = S (IV)]} or uracil I [X = O (V)], III [X = O (VI)] ring. The evaluation of their biol. activity on CCRF-CEM human leukemia cells demonstrated that the most active was II followed by V (mean 50% inhibition of cell proliferation [IC50] 1.7 and 7.9 .mu.M, resp.), while compds. IV and VI were inactive, as were uracil, thiouracil, and 5,6-dimethyluracil, the pyrimidine moieties of compds. II, IV-VI. For comparison, the IC50 of the ref. substance, the cell-permeable C2-ceramide, was 31.6 .mu.M. Compds. II and V and C2-ceramide were able to trigger apoptosis, as shown by the occurrence of DNA and nuclear fragmentation, and to release cytochrome c from treated cells. The treatment of female CD-1 nu/nu athymic mice bearing a WiDr human colon xenograft with the most active compd. II at 2, 10, 50, and 200 mg/kg i.p. daily for 10 days resulted in an antitumor effect that was equiv. at 50 mg/kg or superior (200 mg/kg) to that of cyclophosphamide, 20 mg/kg i.p. daily, delivered on the same schedule, with markedly lower systemic toxicity. In conclusion, the present study demonstrates that the new ceramide analogs II and V are characterized by in vitro and in vivo antitumor activity and low toxicity.
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:78368 CAPLUS
DOCUMENT NUMBER: 134:131369
TITLE: process for the preparation of ceramide analogs and their use as antitumor agents

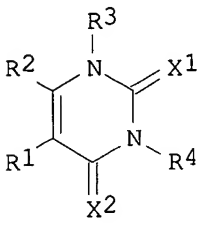
INVENTOR(S): Macchia, Bruno; Balsamo, Aldo; Macchia, Marco; Del Tacca, Mario; Danesi, Romano
PATENT ASSIGNEE(S): Bracco S.p.A., Italy
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001007418	A2	20010201	WO 2000-EP7023	20000721
WO 2001007418	A3	20010510		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
IT 1307786	B1	20011119	IT 1999-FI169	19990722
EP 1198458	A2	20020424	EP 2000-956250	20000721
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				

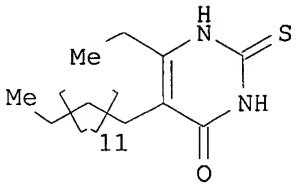
PRIORITY APPLN. INFO.: IT 1999-FI169 A 19990722
WO 2000-EP7023 W 20000721

OTHER SOURCE(S): MARPAT 134:131369

GI



I



II

AB The present invention discloses a process for the prepn. of ceramide analog (I; X1, X2 = O, S; R1, R2 = (CH2)13Me, (un)substituted alkyl, (un)substituted alkylene groups with one or more substituents selected among arom., primary, secondary and tertiary aminic, quaternary ammonium, CO2H, OH, polyoxyalkyl and ethereal groups, amino acids, halogen, saccharidic portions, providing that between R1 and R2 only one is (CH2)13Me; R3, R4 = H, (un)substituted alkyl, (un)substituted alkylene groups with one or more substituents selected among arom., primary, secondary and tertiary aminic, quaternary ammonium, CO2H, OH, polyoxyalkyl and ethereal groups, amino acids, halogen, saccharidic portion) and pharmaceutical formulations for the treatment of tumors. Thus, II was prepd. by the reaction of .beta.-ketoester III, Me(CH2)14CH(COCH2Me)COOCH2Me (obtained by the reaction of Et palmitate and propionyl chloride), with thiourea. II shows IC50 of 1.7 .mu.M in tests against human leukemia cell line called CCRF/CEM.